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PD

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/484,340	06/07/95	SMITH	L 243132000105

ANTOINETTE F KONSKI
MORRISON & FOERSTER
755 PAGE MILL ROAD
PALO ALTO CA 94304-1018

HM22/1228

EXAMINER

HOUTTEMAN, S

ART UNIT	PAPER NUMBER
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1655

34

DATE MAILED:

12/28/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/484,340

Applicant(s)

Smith et al.

Examiner

Scott Houtteman

Group Art Unit

1655



☒ Responsive to communication(s) filed on Dec 3, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle* 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 75-77, 81-83, 88, 98-103, 105-107, 109-111, and 118-147 is/are pending in the application

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 75-77, 81-83, 88, 98-103, 105-107, 109-111, and 118-147 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn. This is Applicants second request under 37 CFR 1.129(a) for removing the finality of an Office action.

2. All previous grounds of rejection have been withdrawn in view of applicant's arguments.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-77, 81-83, 88, 98-103, 105-107 and 109-111, 118-147 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA fragments are tagged with through, an amine linkage, with the fluorophores fluorescein, Texas red, tetra methyl rhodamine and 7-nitro-benzofurazan (see specification page 6 paragraph 2), does not reasonably provide enablement for any chromophore or fluorophore covalently linked to a duplex at any position. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broad. These claims read on the use of any chromophore or fluorophore having any chemical structure, attached at any of the three moieties of a nucleoside, the phosphate, the sugar or the base. Furthermore, any atom of the chromophore or fluorophore can be attached to any atom of the moieties. These claims broadly recite any linkage having any length and any chemical structure.

The description in the specification is relatively limited. Only a single set of fluorophores is exemplified, see page 6, paragraph 2. Furthermore, the specification suggests that only a single method of linking the fluorophores to the nucleic acid. "The chemistry for the coupling of the chromophoric or fluorophoric tags is described in assignee's copending patent applications . . . now abandoned." (Note, it is unclear how an application can be both "copending" and "now abandoned.").

This chemistry is described in US Pat. 4,849,513, 7/1989 (see Information Disclosure Statement filed 3/18/96) which discloses synthesizing a "3'-O-phosphoramidite derivative of a nucleoside analogue containing a protected aliphatic amino group attached to the sugar moiety of the nucleoside." This chemistry will necessarily limit the attachment of the label to the sugar moiety using an amine linkage. The chemical description does not suggest how the label can be attached to any other moiety of the nucleoside.

The chemistry of attaching to another position of the nucleoside would be much different do to the different chemical properties of the bases, purine or pyrimidine, and the phosphate.

Even if a tag is successfully linked to an oligonucleotide there are several other hurdles to be overcome. See, for example, these taken from Menchen et al., US Pat. 5,188,934, col. 1, line 57 to col. 2 line 57. First, it is difficult to find three or more dyes that do not have significantly overlapping emission bands. Second, low fluorescent efficiencies will prevent sufficient material to be added to a sequencing gel. Third, excitation becomes difficult when separate excitation sources for each dye will require a separate light source. Fourth, means by which the fragments are linked to the dyes must not adversely effect the electrophoretic mobilities. Finally, the dyes must be compatible with the chemistry used to manipulate the fragments. For example when the Sanger sequencing method is employed, the dye chemistry must not interfere with the activity of the polymerase, priming or hybridization.

Lacking guidance as to how to determine whether these problems are over come, the skilled artisan must carry out the undue experimentation of brute force trial and error of a myriad number of dyes and dye combinations.

Lacking any enabling disclosure, the skilled artisan would be forced into the undue experimentation of developing these chemistries and testing various tags to determine if the resulting modified nucleic acids will function in the disclosed methods. The development of chemical synthetic methods without any guidance and the testing of the results without any indication as to which will function amounts to undue experimentation.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 75-77, 81-83, 88, 98-103, 105-107 and 109-111, 118-147 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al., Nucleic Acids Research Vol. 13, pages 2399-2412 (1985)(Smith 1985)(see Information Disclosure Statement filed 3/18/96).

7. Claims 75-77, 81-83, 88, 98-103, 105-107 and 109-111, 118-147 are rejected under 35 U.S.C. 102(e) as being anticipated by Smith, US Pat. 4,849,512, 7/1989, effective filing Date 12/20/83 (Smith 1989).

The Smith research article (Smith 1985) and the Smith patent (Smith 1989) contain overlapping subject matter and will be discussed together.

Smith discloses synthesis of fluorescent-labeled oligonucleotides in which the label can be inserted at any position in the oligonucleotide using an amine linkage. See Smith 1989, col. 5, lines 45-58 and Smith 1985 Abstract. During the sequencing procedure the labeled oligonucleotides are placed in a duplex and sets of duplexes and exposed to high intensity fluorescent light as they prime the Sanger termination sequence reactions.

8. Claims 75-77, 81-83, 88, 98-103, 105-107 and 109-111, 118-147 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith 1985 and Smith 1989. Those embodiments

which are not anticipated by the above references are nevertheless make obvious over these references.

For example, Smith 1885 discloses the use of "automation of the DNA sequencing process" which, together with fluorescent-labeled oligonucleotides suggests dyes detectable by exposure to a high-intensity monochromatic light source, for example a laser. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to skill in the art to use a dye detectable by exposure to a high-intensity monochromatic light source such as a laser for the expected benefit of automatic detecting the fluorescent label.

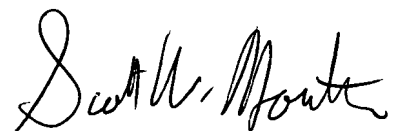
9. Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Technology Center 1600 Fax numbers are (703) 305-3014 and 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott Houtteman whose telephone number is (703) 308-3885. The examiner can normally be reached on Tuesday-Friday from 8:30 AM - 5:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

Scott Houtteman
December 19, 1999


SCOTT W. HOUTTEMAN
PRIMARY EXAMINER